Guidance for Industry

Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics

DRAFT GUIDANCE

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to applicants on endpoints for non-small cell lung cancer (NSCLC) clinical trials submitted to the Food and Drug Administration (FDA) to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications.[2] This guidance is a companion to the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*.[3]

This guidance addresses the FDA's current thinking regarding efficacy endpoints in trials evaluating treatments for lung cancer and considers discussions held at a public workshop (April 15, 2003) and at a meeting of the FDA's Oncologic Drugs Advisory Committee (ODAC) (December 16, 2003).[4] This guidance does not address efficacy endpoints for drugs intended to prevent or decrease the incidence of lung cancer. As the scientific understanding of this disease evolves, this guidance may be revised.

[1] This guidance has been prepared by the Division of Drug Oncology Products and the Division of Biologic Oncology Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] Transcripts are available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm120838.htm and http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4009T1.pdf.

This guidance also does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of lung cancer.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

According to American Cancer Society predictions, during 2010 there will be nearly 222,520 new cases of lung cancer. Lung cancer accounts for approximately 14 percent of all new cancers and it is the leading cause of cancer deaths, accounting for about 28 percent of all cancer deaths. Evaluation of new drugs for the treatment of lung cancer is based on well-conducted and controlled trials assessing appropriate endpoints to establish clinical benefit and support approval.[5]

A. Endpoints Supporting Past Approvals

For regular approval (section 505(d) of the Federal Food, Drug, and Cosmetic Act), it is critical that the applicant show direct evidence of clinical benefit or improvement in an established, validated surrogate for clinical benefit. FDA's accelerated approval regulations, promulgated in 1992 (21 CFR part 314, subpart H, and 21 CFR part 601, subpart E), allow use of a surrogate endpoint that is reasonably likely to predict clinical benefit for approval of drugs or biological products that are intended to treat serious or life-threatening diseases and that provide meaningful therapeutic benefit over existing treatments (e.g., either demonstrate an improvement over available therapy or provide therapy where none exists).[6]

In the past, three commonly used efficacy endpoints in trials assessing treatments of lung cancer were overall survival (OS), time to progression (TTP) or progression-free survival (PFS), and objective tumor response rates (ORR) (see Table 1). The majority of drug approvals for NSCLC have been based on significant improvement in OS, which is an optimal endpoint because the measurement is accurate and represents direct clinical benefit to the patient. Similarly, reduction in patient tumor-related symptoms can also demonstrate direct clinical benefit and can support regular approval.

[5] Refer to the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* for information regarding regulatory requirements for effectiveness.

[6] See Johnson, JR, G Williams, R Pazdur, 2003, Endpoints and United States Food and Drug Administration Approval of Oncology Drugs, J Clin Oncol, 21:1404-1411; and Dagher, R, J Johnson, G Williams, P Keegan, R Pazdur, 2004, Accelerated Approval of Oncology Products: A Decade of Experience, JNCI, 96:1500-1509.

When the observed differences in TTP or PFS are of a substantial magnitude, then TTP or PFS may be evidence of treatment benefit that is reasonably likely to predict an effect on overall survival in support of accelerated approval. Similarly, we consider demonstration of clinically meaningful durable ORR alone to be a surrogate endpoint reasonably likely to predict clinical benefit and it has only been used as the basis for accelerated approval for advanced NSCLC.

However, careful consideration is necessary in the use of TTP or PFS, or ORR as endpoint for efficacy evaluation and regulatory decision. The criteria for disease progression and tumor response are often poorly defined, not rigorously evaluated, and potentially introduce bias particularly when evaluated in open-label trials. Furthermore, primary lung tumors and regional nodal disease frequently have ill-defined borders that can be difficult to accurately and reproducibly measure radiographically. Therefore, confidence in tumor measurement-based outcomes depends on the frequency of assessments as well as clear, objective criteria for defining disease progression, which may include clinical as well as radiological assessments. Substantial numbers of missing tumor assessments can potentially overestimate or underestimate treatment differences. Treatment effects on ORR have not been demonstrated to reliably predict corresponding effects on survival in NSCLC. In certain circumstances, such as when clinical trials have shown that ORR correlated with well-documented improvements in patient tumor-related symptoms (e.g., photodynamic therapy for treatment of obstructing endobronchial therapy), ORR has supported regular approval.

Patient-reported outcome (PRO) measures of tumor-related symptoms and functioning can represent direct measures of treatment benefit if demonstrated to be well-defined and reliable assessments of a clinically meaningful concept or set of concepts and if evaluated in well-conducted, placebo-controlled or double-blinded, randomized trials.[7] Well-defined and reliable assessments include those that have documented evidence of content validity, construct validity, reliability, and ability to detect change in addition to established methods for interpreting trial results.[8] Well-conducted clinical trials include endpoint assessment at a frequency that corresponds to the trial objectives, protocols that minimize unintentional unblinding, and prespecified statistical strategies for handling missing data, particularly at or near the time of disease progression.

[7] See the transcripts of the Oncologic Drugs Advisory Committee Endpoints in Clinical Cancer Trials and Endpoints in Lung Cancer Clinical Trials, December 16, 2003, pp 188-368 (http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4009T1.pdf).

[8] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Table 1: Regulatory Experience With New Drug Approvals for the Treatment of NSCLC

Drug	Trial Design	Approval Endpoints
First-Line Inoperable/Metastatic NSCLC		
Vinorelbine monotherapy	Open-label, randomized, active-controlled trial vs. 5FU/leucovorin	OS, ORR
Vinorelbine in combination with cisplatin	Open-label, randomized, active-controlled trial vs. cisplatin	OS, ORR
Docetaxel in combination with cisplatin	Open-label, randomized, active-controlled trial, docetaxel/cisplatin vs. vinorelbine/cisplatin	OS, TTP, ORR
Gemcitabine in combination with cisplatin	(1) Open-label, randomized, active-controlled trial vs. gemcitabine (2) Open-label, randomized, active-controlled trial, gemcitabine + cisplatin vs. etoposide + cisplatin	OS TTP, ORR
Bevacizumab in combination with paclitaxel/carboplatin[1]	Open-label, randomized, active-controlled trial vs. paclitaxel/ carboplatin	OS
Paclitaxel in combination with cisplatin	Open-label, active-controlled, dose-ranging, randomized, three-arm trial, paclitaxel (135 mg/m^2)/cisplatin vs. paclitaxel (250 mg/m^2)/cisplatin vs. etoposide/cisplatin	TTP, ORR, OS
Pemetrexed in combination with cisplatin[1,2,3]	Open-label, active-controlled, randomized trial; pemetrexed/cisplatin vs. gemcitabine/cisplatin	OS
Maintenance Therapy		
Pemetrexed in patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy[1]	Randomized, double-blind, placebo-controlled trial	OS
Erlotinib in patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy	Randomized, double-blind, placebo-controlled trial	OS
Second-Line NSCLC		
Docetaxel	Randomized, placebo-controlled trial, docetaxel vs. best supportive care	OS, TTP, ORR
Erlotinib	Randomized, placebo-controlled trial, erlotinib vs. best supportive care	OS, TTP, ORR
Pemetrexed[1,2]	Randomized, open-label trial vs. docetaxel	Durable ORR, Decreased Toxicity
Third-Line NSCLC		
Erlotinib	Randomized, placebo-controlled trial Erlotinib vs. best supportive care	OS, TTP, ORR
Gefitinib[2,4]	Single-arm trial	Durable ORR
Partially or Completely Obstructing Endobronchial Tumor NSCLC and Microinvasive Endobronchial NSCLC in Nonsurgical Candidates		
Porfimer sodium and photodynamic therapy	Randomized, open-label, active-controlled trial vs. YAG laser	Improvement in disease-related symptoms

[1] Limited to non-squamous, non-small cell lung cancer.
[2] Accelerated approval.
[3] Because the approval was based on a subgroup of patients, confirmatory evidence in the subgroup from an on-going study was required under the accelerated approval.
[4] Subsequent studies did not confirm clinical benefit; indication will be withdrawn in 2011 (press release http://www.astrazeneca-us.com/search/?itemId=12045633 accessed March 11, 2011).

B. Summary of Workshop and Advisory Committee Discussions

As mentioned, the American Society of Clinical Oncology (ASCO) and the FDA held a public Lung Cancer Endpoints workshop on April 15, 2003, with participants that included representatives from the FDA, ASCO, the National Cancer Institute, academia, advocacy groups, and industry.[9] The discussions in this workshop dealt mainly with advanced and metastatic NSCLC and included pros and cons of using OS, tumor assessment-based endpoints, and PRO measures in evaluating drugs for marketing approval. These discussions recognized that although ORR is a commonly used endpoint, it does not correlate with OS. The clinical significance of small differences in TTP may be unclear, especially when evaluating toxic therapy. TTP is subject to ascertainment bias in open-label trials, and bias can occur if follow-up schedules are asymmetric among trial arms.

Assessment of disease progression at frequent intervals is labor intensive and can be expensive. PRO measures can be important clinical benefit endpoints, particularly in a predominantly symptomatic disease such as NSCLC. However, adequate evaluation of treatment effect based on PRO measures involves blinded, randomized trials using instruments that reliably and validly measure the concepts that define a treatment benefit in the targeted clinical trial population with response options and a recall period that have been demonstrated to be appropriate and interpretable in the subset of patients studied. Analytical challenges, including sensitive but uninterpretable instruments or large amounts of missing data, pose additional difficulties in evaluating an experimental therapy based on PRO data. OS is considered the most appropriate endpoint that is definitive and easy to determine. An observed OS benefit in a well-conducted, randomized trial can be directly attributed to the experimental therapy.

Subsequent to the above-mentioned public workshop, an ODAC meeting was held on December 16, 2003, in which the workshop discussions regarding lung cancer endpoints were presented to the committee.

(1) The committee voted 17 to 2 that since no drug was approved for the adjuvant treatment of NSCLC, hypothetically disease-free survival can be a reasonable endpoint to evaluate new therapy in an adjuvant setting.

(2) As of the date of the meeting, approval for the treatment of metastatic NSCLC generally has been based on demonstration of improvement in overall survival. The committee considered the use of tumor-based time-to-event endpoints as the primary endpoint for either regular or accelerated approval. The committee recommended that the tumor-based endpoint of PFS is preferable to TTP, since PFS includes deaths particularly when there are missing assessments. The uncertainties in measuring PFS were recognized (e.g., indirect measure, unclear clinical meaning of small differences in PFS, the noise and variability in the assessments caused by imaging or timing of assessments, missing and unevaluable data). The committee voted 11 to 8 that PFS may be used as an endpoint to evaluate drug effect in metastatic disease for consideration of regular approval.

[9] See the workshop summary: American Society of Clinical Oncology/FDA Lung Cancer Endpoints Workshop, April 15, 2003, (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm120838.htm).

(3) Regarding the evaluation of drug effect in inoperable or locally advanced disease, the consensus of the committee (vote of 15 to 3) was that an effect on PFS should not be considered sufficient to support regular approval and that new drugs should be evaluated based on OS. To consider differences in PFS as the basis for accelerated approval, the committee was of the opinion that the treatment differences based on PFS had to be substantial (e.g., 3 months or more). It was also recognized that PRO endpoints, such as delay in symptom progression, are important and that better tools are needed to minimize bias and to define what constitutes a benefit.

(4) The committee also discussed the challenges in using noninferiority trial designs with OS and PFS endpoints. A trial with a noninferiority hypothesis can be considered only if the active control has established efficacy, the active control effect size can be estimated for patients with the indication under consideration, and the percent of active control effect size to be retained can be prespecified.[11] The effect size of the active control on the primary endpoint of interest should be established based on meta-analysis of historical, randomized trials. It is not possible to prespecify the percent of active control effect size to be retained when the active control effect size is not well established. When considering trials with a noninferiority hypothesis, an assumption that should be assessed is the constancy of the treatment effect over time attributed to the active comparator. Because medical practice, clinical trial conduct, the timing of tumor progression assessments, the radiological modalities used, and the criteria and definition for assessing progression that have evolved over time vary between trials especially when trials are conducted in different geographic regions, it will be difficult to verify the constancy assumption with PFS as primary endpoint.

Since the 2003 meeting, we have continued to use OS as the primary endpoint for NSCLC.

III. RECOMMENDATIONS

We consider OS to be the standard clinical benefit endpoint that should be used to establish efficacy of a treatment in patients with advanced and metastatic NSCLC. However, other endpoints can be considered for regulatory decision based on the population and risk-benefit profile of a drug. We also recognize that it may not always be feasible to conduct trials separately in patients with locally advanced and metastatic NSCLC.

Consideration of PFS as the primary endpoint for demonstration of efficacy for drug approval is based on the magnitude of the effect and the risk-benefit profile of the drug. Because of the subjectivity in the measurement of PFS assessments and the fact that the assessments depend on frequency, accuracy, reproducibility, and completeness, the observed magnitude of effect should be substantial and robust.

[11] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Planned interim efficacy analyses based on OS may be appropriate. However, interim analyses of PFS before completion of patient accrual are discouraged. Early interim analyses of PFS that cross a stopping boundary often overstate the magnitude of the effect. An interim PFS analysis is unlikely to provide an accurate or reproducible estimate of the treatment effect size because of inadequate follow-up, missing assessments, disagreements between radiological reviewers, and/or disagreements between investigator and independent assessments. Stopping a trial based on interim PFS results that may not be verifiable after adjudication can render the trial results un-interpretable. In addition, a statistically significant difference in PFS of short duration may not be deemed clinically meaningful.

We encourage the development of well-defined and reliable PRO instruments that capture the essential treatment benefit concepts in the targeted population. To interpret PRO data, it is generally useful to include a means to gather a complete record of all doses of concomitant medications, such as analgesics, antidepressants, antiemetics, and antidiarrheals, to differentiate anticancer treatment effect from the effects of concomitant medication. This can be accomplished using PRO instruments (i.e., event logs) or other assessment tools. We will review the adequacy of all PRO measures based on the principles outlined in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Recent studies reported in literature and drug approvals suggest that NSCLC is a heterogeneous disease with varying treatment effects (efficacy and toxicity) particularly among different histological types of NSCLC.[12] We recommend that clinical trials be prospectively designed to evaluate such differences in treatment effect.

Although general principles outlined in this guidance should help applicants select endpoints for marketing applications, we recommend that applicants meet with the FDA before submitting protocols intended to support NDA or BLA marketing applications. These meetings will include a multidisciplinary FDA team of oncologists, statisticians, clinical pharmacologists, and often external expert consultants. Applicants can submit protocols after these meetings and request a special protocol assessment that provides confirmation of the appropriateness of endpoints and protocol design to support drug marketing applications.[13] Marketing approval depends not only on the design of clinical trials, but on FDA review of the results and data from all trials in the drug marketing application.

[12] See for example the Pemetrexed product label at Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

[13] See the guidance for industry *Special Protocol Assessment*.

APPENDIX 1: TUMOR MEASUREMENT DATA COLLECTION[14]

The following are important considerations for tumor measurement data. We recommend that:

- The case report form (CRF) and electronic data document the target lesions identified during the baseline visit before treatment. Retrospective identification of such lesions would not be considered reliable.

- Tumor lesions be assigned a unique identifying letter or number. This assignment provides differentiation among multiple tumors occurring at one anatomic site and the matching of tumors measured at baseline and tumors measured during follow-up.

- A mechanism be in place that ensures complete data collection at critical times during follow-up. The CRF should ensure that all target lesions are assessed at baseline and that the same imaging or measuring method is used for all tests required at baseline and follow-up.

- The CRF contains data fields that indicate whether scans were performed at each visit.

- A zero be recorded when a lesion has completely resolved. Otherwise, disappearance of a lesion cannot be differentiated from a missing value.

- Follow-up tests provide for timely detection of new lesions both at initial and new sites of disease. The occurrence and location of new lesions should be recorded in the CRF and in the submitted electronic data.

[14] For the purposes of this appendix, *tumor data* refers to data in SAS transport files, not images. Generally, images are not submitted to the NDA or BLA, but can be audited by the FDA during the review process.

APPENDIX 2: ISSUES TO CONSIDER IN PFS ANALYSIS

The protocol and statistical analysis plan (SAP) should detail the primary analysis of PFS. This analysis should include a detailed description of the endpoint, appropriate modalities for evaluating tumors, and procedures for minimizing bias, such as procedures for an independent review committee (IRC). One or two secondary analyses should be specified to evaluate anticipated problems in trial conduct and to assess whether results are robust. The following important factors should be considered.

- **Definition of progression date.** In survival analyses, the exact death date is known. In PFS analyses, the exact progression date is unknown. The following two methods can be used for defining the *recorded progression date (PDate)* used for PFS analysis.

  1. PDate assigned to the first time at which progression can be declared.

     – For progression based on a new lesion, the PDate is the date of the first observation that the new lesion was detected.

     – If multiple assessments based on the sum of target lesion measurements are done at different times, the PDate is the date of the last observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements.

  2. PDate as the date of the protocol-scheduled clinic visit immediately after all radiological assessments (which collectively document progression) have been done.

- **Definition of censoring date.** Censoring dates are defined in patients with no documented progression before data cutoff or dropout. In these patients, the censoring date is often defined as the last date on which progression status was adequately assessed. One acceptable approach uses the date of the last assessment performed. However, multiple radiological tests can be evaluated in the determination of progression. A second acceptable approach uses the date of the clinic visit corresponding to these radiological assessments.

- **Definition of an adequate PFS evaluation.** In patients with no evidence of progression, censoring for PFS often relies on the date of the last *adequate tumor assessment.* A careful definition of what constitutes an adequate tumor assessment includes adequacy of target lesion assessments and adequacy of radiological tests both to evaluate nontarget lesions and to search for new lesions.

- **Analysis of partially missing tumor data.** Analysis plans should describe the method for calculating progression status when data are partially missing from *adequate tumor assessment* visits.

- **Completely missing tumor data.** Assessment visits where no data are collected are sometimes followed by death or by assessment visits showing progression. In other cases, the subsequent assessment shows no progression. In the latter case, it may seem appropriate

to continue the treatment and continue monitoring for progression. However, this approach treats missing data differently depending upon subsequent events and can represent informative censoring. Another possible approach is to include data from subsequent PFS assessments. This can be appropriate when evaluations are frequent and when only a single follow-up visit is missed. Censoring at the last adequate tumor assessment can be more appropriate when there are two or more missed visits. The SAP should detail primary and secondary PFS analyses to evaluate the potential effect of missing data. Reasons for dropouts should be incorporated into procedures for determining censoring and progression status. For instance, for the primary analysis, patients going off-study for undocumented clinical progression, change of cancer treatment, or decreasing performance status can be censored at the last adequate tumor assessment. The secondary sensitivity analysis would include these dropouts as progression events. Although missed visits for progression can be problematic, all efforts should be made to keep following patients for disease progression irrespective of the number of visits missed.

- **Progression of nonmeasurable disease.** When appropriate, progression criteria should be described for each assessment modality (e.g., CT scan, bone scan). Scans documenting progression based on nonmeasurable disease should be verified by a blinded review committee and be available for verification by the FDA.

- **Suspicious lesions.** An algorithm should be provided for evaluating and following indeterminate lesions for assignment of progression status at the time of analysis.

APPENDIX 3: EXAMPLE TABLE FOR PRIMARY PFS ANALYSIS

An example of a censoring scheme that can be used is provided in the following table.

Table X. PFS (progression as defined in the protocol)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	Censored
New anticancer treatment started	Date of last progression assessment with no documented progression	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with no documented progression	Censored

APPENDIX 4: EXAMPLE TABLES FOR PFS SUPPORTIVE ANALYSIS

Sensitivity analyses can be helpful in determining whether the PFS analysis is robust. However, these sensitivity analyses are exploratory and supportive of the results of the primary analysis, and efficacy may not be claimed based on sensitivity analysis alone. Different sensitivity analyses can be described in tables that specify how dates of progression events and dates for censoring of progression data can be assigned. The following three tables describe examples of three different sensitivity analyses.

a. Table A represents a sensitivity analysis that only includes well-documented and verifiable progression events. Other data are censored. In Table A, the progression dates are:

- Based only on radiological assessments verified by an IRC. *Clinical progression* is not considered a progression endpoint.
- Assigned to the first time when tumor progression was noted.
- The date of death when the patient is closely followed. However, deaths occurring after two or more missed visits are censored at the last visit.

Table A. PFS 1 (includes documented progression only)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions	Censored

The sensitivity analysis in Table B corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates. However, this approach can introduce bias if the progression occurred closer to the last visit, particularly in an open-label trial. This approach can be suitable in blinded, randomized trials.

Table B. PFS 2 (uniform progression and assessment dates)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Date of next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last visit with adequate assessment	Censored

b. The sensitivity analysis in Table C evaluates PFS according to the investigator's assessment. However, this approach can introduce bias if the progression occurred closer to the last visit, particularly in an open-label trial. This approach can be suitable in blinded, randomized trials.

Table C. PFS 3 (includes investigator claims)

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Randomization	Censored
Progression documented between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Investigator claim of clinical progression	Scheduled visit (or next scheduled visit if between visits)	Progressed
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Progressed
Death after an extended lost-to-follow-up time (two or more missed assessments)	Last visit with adequate assessment	Censored